B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,423	08/25/2003	Sergei G. Bavykin	21416-94731	5272

23644 7590 03/21/2006

BARNES & THORNBURG, LLP
P.O. BOX 2786
CHICAGO, IL 60690-2786

EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/647,423	BAVYKIN ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,16,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12,16,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II, claims 10-20 and 22 and further election of SEQ ID NOS: 74, 75, 86, 87, 88, 89, 90, 91, 126, 127 in the response filed on 02/23/2006 is noted. Claims 1-9 and 21 are withdrawn; claims 13-15, 18-19 and 22 are cancelled.

Priority

It is noted in the response filed 02/23/2006 that the priority claim has been amended so as to claim priority to provisional application 60/336,319 (filed November 2, 2001).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "the microchip" in line 3. There is insufficient antecedent basis for this limitation in the claim. This rejection could be overcome by substituting the words “the microarray” in place of “the microchip”.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation "wherein the sequence of the oligonucleotide probe is reversed" is unclear. Strictly reversing the sequence of, for example, SEQ ID NO: 74 gives the sequence ACGAGAATACTTCAATCGCC, while the *reverse complement* gives the sequence TGCTCTTATGAAGTTAGCGG. It is not clear which is intended. It is also confusing because neither of the resulting sequences are recited in claim 16, so claim 17 cannot depend from claim 16. If Applicant intends to claim the reverse complements of the sequences listed in claim 16, the rejection may be overcome by writing claim 17 in independent form and using the language "wherein the sequence of the oligonucleotide probe is the full reverse complement of the sequence of claim 16". For purposes of examination, the interpretation will be that Applicant intends to claims the full reverse complement of the probe of claim 16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-12, 16, 17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsuhashi (US Pat 5,580,971) in view of Ash et al (1991), Chee et al

(1996), Ash et al (1992) and Genbank Accession Nos (GI Nos) 3929652, 8452887, 3929664, 3929662, 927390, and 1149455.

With regard to claims 10 and 20, Mitsuhashi teaches a method comprising placing on a microchip oligonucleotide probes targeted to rRNA sequences (see figure 2), providing conditions for hybridization of the probes with rRNA from the sample (see column 1 line 50 through column 2 line 20), and analyzing hybridization signals in the microchip from which the particular isolate is detected (see column 2 lines 35-45). In this case, the "microchip" (which is not explicitly defined or otherwise limited by Applicant's disclosure) is a microtiter plate (see column 1 lines 50-60). Mitsuhashi does not teach probes corresponding to the specific oligonucleotide probes of claim 10.

Ash teaches a method for the discrimination among *B. anthracis, B. cereus, B. mycoides,* and *B. thuringiensis* based on 16s rRNA sequencing, wherein at least one mismatch is sufficient to discriminate among these members (see Table 2). In fact, at least two of the mismatches (see Table 2, position 92/94 and position 1,005 and see Figure 1) correspond to the mismatches used by Applicant in the SEQ ID NO 86/87 and 74/75 probe pairs. Ash does not teach the specific oligonucleotide probes of claim 10, or the use of a microchip, hybridization, or analysis of hybridization signals for distinguishing among the members of the *B. cereus* group.

Chee teaches the use of oligonucleotide microchip arrays for the discrimination of sequences having a single nucleotide mismatch (see page 611, column 1, 1st sentence of 1st full paragraph, and see Figure 1). Chee does not teach the use of such an array for the discrimination among members of the *B. cereus* group, but does teach

that "[t]he methods described are generic and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability" (see abstract). Chee does not teach the use of the specific oligonucleotide probes of claim 10.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to combine the discriminating polymorphisms taught by Ash with the oligonucleotide arrays taught by Chee to arrive at the microarray of claim 10 in order to discriminate among species based on rRNA hybridization as taught by Mitsuhashi. Motivation to do so is clear since the polymorphisms taught by Ash are single nucleotide mismatches, and Chee teaches that the array is able to detect polymorphisms "with single-base resolution" (see abstract). Chee also teaches that hybridization-based methods using oligonucleotide microchips have higher throughput capacity than conventional sequencing based methods such as those used by Ash et al (see Chee page 612, column 3, 2nd full paragraph).

Ash teaches that "[s]mall-subunit rRNA is now recognized as a powerful molecular chronometer" and Applicant agrees (on page 2 of the specification of provisional application 60/336,319 upon which priority of the instant application is based) that "[h]ybridization analysis of the 16S rRNA is a well established method of microbial identification" (references omitted). Since Ash also teaches that "[o]nly 11 base substitution points on the sequences were identified" (comparing the 16s rRNA sequences of *B. anthracis, B. cereus, B. mycoides,* and *B. thuringiensis*, see page 345, column 1), one of ordinary skill would clearly have been motivated to use these

polymorphisms when designing discriminating oligonucleotide probes.

Chee teaches the use of discriminating single nucleotide polymorphisms using a matched set of probes in which the variant nucleotide resides in the middle of the probe (see figure 1, panels A and B). This is based on the sound scientific reasoning that placing the mismatch in the middle of the probe would minimize the length of continuous complementarity, thus resulting in the lowest melting temperature between probe and mismatched target, thus maximizing the difference in melting temperature between perfectly matched and mismatched sequences. Therefore, one of ordinary skill in the art would be motivated to design a oligonucleotide probe microarray in which the variant nucleotides identified by Ash would reside in the middle, resulting in the claimed microarray comprising probes corresponding to the SEQ ID NO 86/87 and 74/75 probe pairs. Note that while one of ordinary skill might have ended up with probes with minor differences from the SEQ ID NO 86/87 and 74/75 probe pairs (i.e. with one or more additional or fewer nucleotides at either end), such minor differences would not be considered unobvious in view of *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), in which the Court of Appeals for the Federal Circuit stated regarding structural or functional homologs:

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties"

Since the claimed probes simply represent functional homologues of probes that would have been obvious to one of skill in the art at the time, the claimed microarray is *prima facie* obvious in the absence of secondary considerations.

With regard to claims 11 and 12, the arrangement of oligonucleotide probes on the array is simply a matter of design choice (see MPEP 2144.04, VI, C Rearrangement of parts). In the absence of secondary considerations, the arrangement of oligonucleotide probes on the array would not affect the performance of the microarray in terms of its ability to discriminate among the various *Bacillus* strains.

With regard to claims 16 and 17, since the microarray of claims 10-12 and 20 are *prima facie* obvious as discussed above, the probes on the array are also *prima facie* obvious, since one could not construct the microarray without also synthesizing the probes.

With regard to all claims, it is further noted that all of the sequences of SEQ ID NOS 88-91 and 126-127 were known in the prior art to be contained within either the 16s or 23s rRNA sequences from *Bacillus* strains as evidenced by Genbank Accession Nos (GI Nos) 3929652, 8452887, 3929664, 3929662, 927390, and 1149455. The teachings of Ash (1991, 1992) as to the relative rarity of polymorphisms in these sequences among members of the *B. cereus* group would provide clear motivation to one of ordinary skill to choose the polymorphisms represented by said SEQ ID NOS to distinguish members of the *B. cereus* group as discussed above.

SEQ ID NO 88 (reverse complement):

```
>gi|3929652|emb|Y18473.1|BTH18473  Bacillus thuringiensis 16S rRNA gene, strain WS2623
          Length=1474

 Score = 40.1 bits (20),  Expect = 4e-04
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Plus

Query  1     GCTTCTCCTTCGGGAGCAGA  20
             ||||||||||||||||||||
Sbjct  983   GCTTCTCCTTCGGGAGCAGA  1002
```

SEQ ID NO 89 (reverse complement):

```
>gi|3452887|gb|AF155957.1|AF155957  Bacillus mycoides strain 10206 16S ribosomal RNA gene, partial
          sequence
          Length=1508

 Score = 40.1 bits (20),  Expect = 6e-04
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Plus

Query  1     GCTTCCCCTTCGGGGGCAGA  20
             ||||||||||||||||||||
Sbjct  1021  GCTTCCCCTTCGGGGGCAGA  1040
```

SEQ ID NO 126:

```
>gi|3929664|emb|Z84594.1|BTH84594  Bacillus thuringiensis 16S rRNA gene, strain WS 2617
          Length=2175

 Score = 40.1 bits (20),  Expect = 4e-04
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     TTTGGGCTATGTTCCGTTTC  20
             ||||||||||||||||||||
Sbjct  1924  TTTGGGCTATGTTCCGTTTC  1905
```

SEQ ID NO 127:

```
>gi|3929662|emb|Z84592.1|BCE84592  Bacillus mycoides 16S rRNA gene, strain DSM 2048T
          Length=632

 Score = 40.1 bits (20),  Expect = 0.027
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     TTTGGGCTAGATTCCGTTTC  20
             ||||||||||||||||||||
Sbjct  580   TTTGGGCTAGATTCCGTTTC  561
```

SEQ ID NO 90:

```
>gi|927390|emb|X89895.1|BT16S23S  B.thuringiensis DNA for 16S and 23S rRNA and spacer region
          Length=2978

 Score = 40.1 bits (20),  Expect = 0.027
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     CAGCTCAGCCTTCACGATAA  20
             ||||||||||||||||||||
Sbjct  1768  CAGCTCAGCCTTCACGATAA  1749
```

SEQ ID NO 91:

```
>gi|1149455|emb|X94448.1|BC16S23SD  B.cereus 23S rDNA and 16S-23S spacer region
          Length=2978

 Score = 40.1 bits (20),  Expect = 0.027
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     CAGCTCAGCCTTTACGATAA  20
             ||||||||||||||||||||
Sbjct  1767  CAGCTCAGCCTTTACGATAA  1748
```

Double Patenting

Claims 10, 11, 12, 16, 17 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9, 10, and 12 of copending Application No. 10/287,455. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9 and 10 of the '455 case are drawn to a microarray comprising sequences identical to SEQ ID NOS: 74, 75, 86, 87, 88, 89, 90, 91, 126, 127. Claim 12 of the '455 case is drawn to probes with identical sequence to SEQ ID NOS: 74, 75, 86, 87, 88, 89, 90, 91, 126, 127.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

JEFFREY FREDMAN
PRIMARY EXAMINER
3/16/06